A CHIRAL SYNTHESIS OF THE KEY INTERMEDIATE OF 1β -METHYLCARBAPENEM ANTIBIOTIC#

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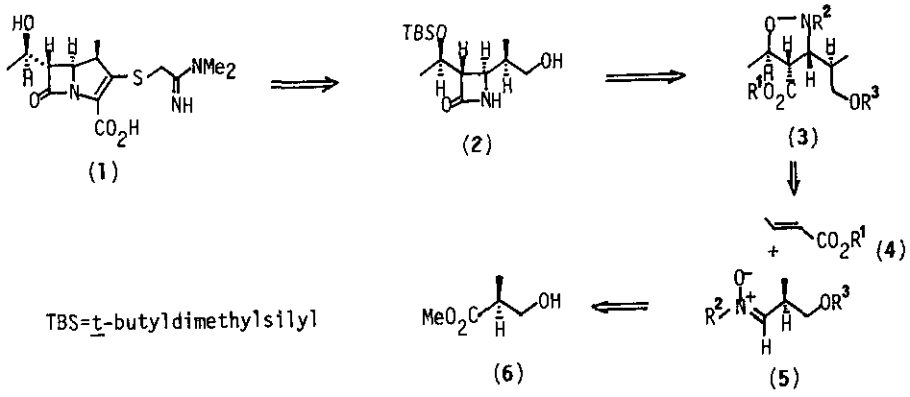
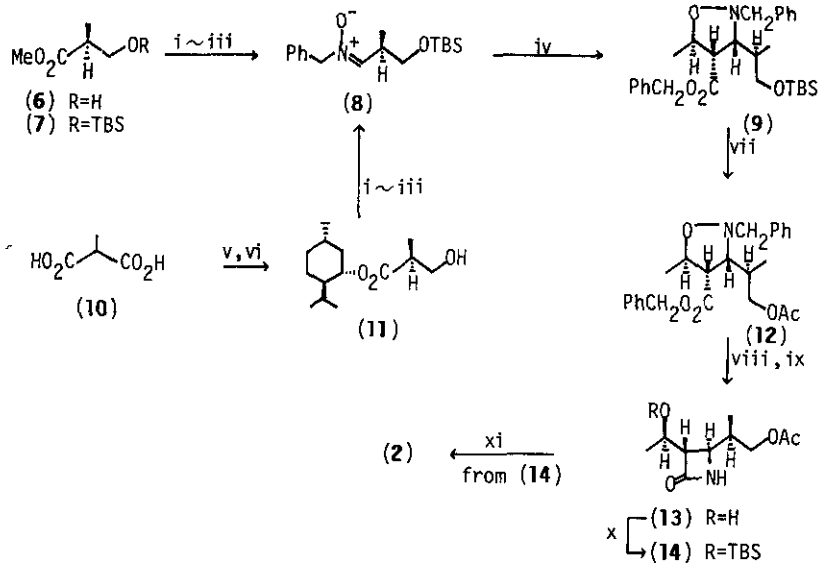
Abstract —— The synthetic intermediate, (-)-(3S,4R)-3-[(1R)-1-t-butyldimethylsilyloxyethyl]-4-[(1R)-1-hydroxymethylethyl]azetidin-2-one (2), of 1β -methylcarbapenem antibiotic was synthesized from (S)-methyl 3-hydroxy-2-methylpropionate through the intermolecular nitrone 1,3-dipolor cycloaddition.

Thienamycin and related naturally occurring carbapenems possess potent broad-spectrum antibacterial property[1] but they suffer serious disadvantages that they are chemically unstable and readily metabolized by renal dehydropeptidase-I (DHP-I). Recently Merck researchers found that introduction of the β-methyl substituent at the C-1 position of nucleus resulted in an extraordinary increase of stability; 1β -methylcarbapenem such as (1) showed excellent antibiotic activity.[2] Therefore the key intermediate having four contiguous chiral centers is the focus of current synthetic attention.[3] We planned the synthesis of the chiral intermediate (2)[3i] from the isoxazolidine derivative (3), which could be prepared by the 1,3-dipolar cycloaddition between crotonate (4) and the nitrone (5) derived from (S)-methyl 3-hydroxy-2-methylpropionate (6) and wish to communicate the result.[4]



Scheme 1

After protection of the commercially available ester (**6**) with t-butyldimethylsilyl group (98 % yield), the ester (**7**) was reduced with diisobutylaluminum hydride in a mixture of dichloromethane and 1,2-dimethoxyethane at -78°C. The resulting aldehyde was condensed with N-benzylhydroxylamine to give the nitrone (**8**), which was subsequently heated in the presence of benzyl crotonate for 10 h in refluxing benzene producing the stereoisomeric mixture of isoxazolidines. One major isomer, (**9**)†, $[\alpha]_D^{26}$+13.23° (c=1.74, $CHCl_3$), was purified by careful hplc separation and the stereochemistry of (**9**), obtained in 23 % overall yield from (**7**), was determined by the transformation into the known intermediate (**2**). The same isoxazolidine (**9**) was also prepared from methylmalonic acid (**10**) as follows.[5] Condensation of (**10**) with d-menthol followed by chlorination of the resulting half ester and reduction with tetra-n-butylammonium borohydride in dichloromethane at -78°C afforded the separable mixture of two epimeric alcohols (**11** and its epimer) in 60 % overall yield in the ratio of about 3:2. The major product (**11**) was converted into the isoxazolidine (**9**), $[\alpha]_D^{24}$+12.5° (c=0.08, $CHCl_3$), according to the same procedures as above.



Reagents and conditions: i, $^tBuMe_2SiCl$, Et_3N, DMAP; ii, DIBAL, CH_2Cl_2, DME, -78°C; iii, $PhCH_2NHOH$, 20°C; iv, $MeCH{=}^tCHCO_2CH_2Ph$, benzene, reflux; v, d-menthol, DCC, DMAP; vi, $(COCl)_2$ then $^nBu_4NBH_4$, CH_2Cl_2, -78°C; vii, Ac_2O, Et_3N, DMAP, $^nBu_4NF$, THF; viii, H_2 (5~6atm), 10% Pd-C; ix, DCC, MeCN, 60°C; x, $^tBuMe_2SiCl$, imidazole, DMF; xi, MeONa, MeOH.

Scheme 2

Exchange of the t-butyldimethylsilyl group of (**9**) with acetoxyl group was carried out by the action of acetic anhydride, triethylamine, 4-dimethylaminopyridine and tetrabutylammonium fluoride in tetrahydrofuran at room temperature. The acetate $(12)^{\dagger}$, $[\alpha]_D^{26}$+31.35° (c=1.90, $CHCl_3$), obtained in 77 % yield (84 % yield based on the consumed starting material), was hydrogenated in the presence of 10 % palladium on activated carbon under hydrogen (5 ∿ 6 atm) and the resulting amino acid was sequentially treated with dicyclohexylcarbodiimide in acetonitrile at 60°C for 5 h to provide the β-lactam $(13)^{\dagger}$, $[\alpha]_D^{25}$-7.55° (c=0.27, $CHCl_3$), in 63% overall yield. Protection of (**13**) using t-butyldimethylsilyl chloride and imidazole in dimethylformamide gave quantitatively the ether $(14)^{\dagger}$, $[\alpha]_D^{24}$-22.37° (c=0.52, $CHCl_3$). Reaction of the acetate (**14**) with sodium methoxide provided in 77 % yield the primary carbinol (**2**), mp 89.5-90.5°C, $[\alpha]_D^{24}$-21.1° (c=0.12, $CHCl_3$) [lit.,[3i] mp 90-91°C, $[\alpha]_D^{20}$-21.7° (c=0.46, $CHCl_3$)], whose spectral data were consistent with those of the authentic compound,[3i] correlated to 1β-methylcarbapenem (**1**).[1,3i]

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† Ir($CHCl_3$) and nmr($CDCl_3$) data: (**9**) ir, 1722 cm^{-1} (C=O); nmr(90 MHz), δ 0.90(9H, s, ^tBu), 0.97(3H, d, J 8.0 Hz, Me), 1.40(3H, d, J 7.0 Hz, Me), and 5.22(2H, s, CH_2Ph); (**12**) ir, 1730 cm^{-1} (C=O); nmr(500 MHz), δ 0.95(3H, d, J 8.0 Hz, Me), 1.42(3H, d, J 7.5 Hz, Me), 1.78(3H, s, OAc) and 5.15 and 5.19 (each 1H, each d, each J 14 Hz, CH_2Ph); (**13**) ir, 3425(NH) and 1760∿1722 cm^{-1} (C=O); nmr (500 MHz), δ1.03(3H, d, J 8.0 Hz, Me), 1.32(3H, d, J 8.0 Hz, Me), 2.08(3H, s, OAc), 2.98(1H, ddd, J 0.3, 2.5 and 8.0 Hz, C_3-H), 3.57(1H, dd, J 2.5 and 9.0 Hz, C_4-H), and 5.97(1H, br s, NH); (**14**) ir, 3420(NH) and 1760∿1730 cm^{-1} (C=O); nmr(500 MHz), δ 0.09(6H, s, $SiMe_2$), 0.88(9H, s, ^tBu), 1.02(3H, d, J 8.0 Hz, Me), 1.23(3H, d, J 8.0 Hz, Me), 2.07(3H, s, OAc), 2.92(1H, ddd, J 0.7, 2.5 and 7.5 Hz, C_3-H), 3.62(1H, dd, J 2.5 and 8.5 Hz, C_4-H), 4.18(1H, quintet, J 7.5 Hz, >CHOTBS), and 5.83(1H, br s, NH).

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